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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,685	04/23/2002	Lars Reinhardt Haaheim	061612-0015	8212

9629 7590 10/04/2005

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EXAMINER	
GABEL, GAILENE	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 10/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/009,685	HAAHEIM, LARS REINHARDT	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29 and 31-46* is/are pending in the application.

4a) Of the above claim(s) *1-20 and 43-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-29 and 31-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-29 and 31-46* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 April 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/15, 6/7 2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *IDS- 6/9, 10/15, 12/5 2003,*.

DETAILED ACTION

Election/Restrictions

Amendment Entry

1. Applicant's election of Group III, claims 21-42, with traverse, filed July 21, 2005 is acknowledged and has been entered. Claims 1-20 and 43-46 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being claims drawn to a non-elected invention. Applicant's supplemental amendment, filed August 11, 2005 is also acknowledged and has been entered. Claims 38 and 39 have been amended. Claim 30 has been cancelled. Accordingly, claims 1-29 and 31-46 are pending. Claims 21-29 and 31-42 are under examination.

Applicant argues that claims 43-45 in Group II should appropriately be included with claims 21-29 and 31-42 in Group III because they share the same or corresponding special technical features, which define a contribution which each of the claimed invention, considered as a whole, makes over the prior art. Applicant specifically contends that the special technical feature of the invention in Group III is the recitation of "by lysis of the lymphocytes".

In response, Applicant's argument is not persuasive because Groups II and III are patentably distinct by virtue of difference in structural and functional requirements between the inventions. Specifically, Group III requires merely a determination of the presence or concentration of newly synthesized antibody in body fluid sample, whereas Group II including claims 43-45 requires a method wherein a series of determinations of

newly synthesized antibodies, are performed to correlate results with reference standards, and depending on comparison of the results with established thresholds, presence of infection can be diagnosed and monitored. The record set forth in the previous restriction requirement clearly indicated that the delineated inventions are in fact patentably distinct each from the other or independent from the other. Accordingly, the restriction requirement is being maintained. Claims 43-45 remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being claims drawn to a non-elected invention, along with claims 1-20 and 46. Claims 1-29 and 31-46 are pending and claims 21-29 and 31-42 are under examination.

Priority

2. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. The priority of the application has been established to be June 14, 1999.

Specification

3. The disclosure is objected to because of the following informalities:

In the specification at page 8, line 21, "pressure or amount of" should be --presence or amount of--.

In the specification at page 11, line 13, "H3N2 IgO" should be "H3N2 IgG".

Appropriate correction is required.

Information Disclosure Statement

4. The information disclosure statement filed December 5, 2003 complies with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has, however, been noted that pages 347 and 351 are part of the Yong Sung Choi reference, but were intentionally excluded from the copy submitted. Accordingly, only the information referred to therein, which excludes that which is set forth in pages 347 and 351, has been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 21-29 and 31-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21 lacks antecedent basis in reciting, "the released target antibodies or parts thereof".

Claim 21 is non-idiomatic and, therefore, confusing in reciting, "whereby to release the synthesized antibodies ..." and "whereby to determine the presence of newly synthesized antibody ..." because it unclear what Applicant intends to encompass by such recitation. Claim 21 is indefinite in being incomplete for omitting essential

structural and functional cooperative relationships of elements and for omitting essential steps, in order to arrive to "determining the presence or amount of newly synthesized antibody" as required by the preamble, such omission amounting to a gap between the steps. See MPEP § 2172.01. It is unclear as to whether "the synthesized antibodies" in lines 5-6 of the claim, are the same as "the released target antibodies" in line 4 of the claim because the structural and/or functional cooperative relationship between these two elements in the claim is not clearly defined. See also claim 22, specifically step iii).

Claim 21 is vague and indefinite in reciting, "detecting the released antibodies or parts thereof *in a sample containing lymphocytes* that have been disrupted" because it appears to imply, but fails to clearly define that the antibodies to be detected are limited to those released from disrupted lymphocytes. Perhaps, Applicant intends, "detecting released antibodies from disrupted lymphocytes contained in a sample".

Claim 21 is confusing in reciting, "lymphocytes which have been disrupted" because it is unclear as to whether disruption of lymphocytes should be part of the method.

Claim 21 is vague and indefinite in reciting, "whereby to release the synthesized antibodies ... associated with said lymphocytes," because it is unclear as to whether the synthesized antibodies are released from the lymphocytes. Additionally, it is also unclear how the released antibodies are "associated" with the lymphocytes since the term "associated" is a subjective term that lacks a comparative basis for defining its metes and bounds. See also claim 22, specifically step ii).

The following is suggested but not required to assist Applicant in obviating indefiniteness issues, "subjecting lymphocytes contained in a sample to disruption, wherein target antibodies or parts thereof are released from the disrupted lymphocytes, detecting the target antibodies or parts thereof released from the lymphocytes in the sample, wherein the presence or amount of released target antibodies or parts thereof from the lymphocytes *provides* or *indicates* or *is representative* of the presence or amount of newly synthesized antibodies in the sample."

Claim 22, step ii) is vague and indefinite in reciting, "whereby to release the synthesized antibodies ... associated with said lymphocytes," because it is unclear as to whether the synthesized antibodies are released from the lymphocytes. Additionally, it is also unclear how the released antibodies are "associated" with the lymphocytes since the term "associated" is a subjective term that lacks a comparative basis for defining its metes and bounds.

Claim 22 is non-idiomatic and, therefore, confusing in reciting, "whereby to release the antibodies ..." and "whereby to determine the presence of newly synthesized antibody ..." because it unclear what Applicant intends to encompass with such recitation. Claim 22 is indefinite in being incomplete for omitting essential structural and/or functional cooperative relationships of elements, i.e. "the newly synthesized antibody" and "the released target antibodies" in step iii) of the claim. It is unclear as to whether "the synthesized antibodies" are the same as "the released target antibodies" claim because the structural and/or functional cooperative relationship between these two elements in the claim is not clearly defined.

The following is suggested but not required to assist Applicant in obviating indefiniteness issues in claim 22, "ii) disrupting said lymphocytes to release target antibodies or parts thereof, and iii) detecting presence or amount of released target antibodies or parts thereof from the lymphocytes, wherein the presence or amount of released target antibodies or parts thereof from the lymphocytes *provides* or *indicates* or *is representative* of the presence or amount of newly synthesized antibodies in the sample."

Claim 29 lacks antecedent basis in reciting, "said solid phase".

Claim 29 lacks antecedent basis in reciting, "said solid phase".

Claim 35 is indefinite in merely reciting "a use of lymphocytes" in the method without any active, positive steps delimiting how this use is actually practiced. Perhaps, Applicant intends, "The method ... further comprising isolating the lymphocytes directly from the sample".

Claim 37 is indefinite in reciting, "ELISA". Acronyms or abbreviations must be fully defined and recited at least one time in a set of claims.

Claim 38 lacks antecedent basis in reciting, "said solid phase", first and second occurrence.

Claim 38 is confusing because it is unclear how and why the "target antibodies" that need to be detected would have been immobilized on solid phase in a solid phase assay, since it is the "target antibodies" that are in need of detection and quantitation. It appears that one or more antigens that recognize the target antibodies should be immobilized into solid phase for contact with target antibodies for detection. Perhaps

Applicant intends, "wherein one or more antigens which recognize target antibodies are immobilized into solid phase, for contacting with released target antibodies and detecting newly synthesized antibodies."

Claim 39 lacks antecedent basis in reciting, "said solid phase", first and second occurrence.

Claim 39 is confusing because it is unclear how and why the "target antibodies" that need to be detected would have been immobilized on solid phase in a solid phase assay, since it is the "target antibodies" that are in need of detection and quantitation. It appears that one or more antibodies that recognize the target antibodies should be immobilized into solid phase for contact with target antibodies for detection. Perhaps Applicant intends, "wherein one or more antibodies which recognize target antibodies are immobilized into solid phase, for contacting with released target antibodies and detecting newly synthesized antibodies."

Claim 40 is vague and indefinite because it is unclear how the "soluble substrate" is used for the detection step to yield a spectrophotometric signal. Is the target antibody labeled with an enzyme for reaction with soluble substrate to hence, produce a spectrophotometric signal. Please clarify.

Claim 40 provides for the use of "soluble substrate", but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 41 is vague and indefinite because it fails to clearly define how the negative control is used in the context of the recited method. Please clarify.

Claim 41 provides for the use of "negative control", but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 42 is vague and indefinite because it fails to clearly define how the "multiple solid phases" are employed in the context of the recited method. Does Applicant intend for the different antigens to have specificity for the target antibodies to be detected.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 21-23, 26, 33, 35, and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by Choi (Biosynthesis and Secretion of Immunoglobulins, Immunoglobulins, pages 345, 346, 348-351 (1981)).

Choi provides methods used to study production of newly synthesized antibodies (biosynthesis of immunoglobulins) in lymph node samples in response to immunogen exposure (see Introduction). Choi teaches obtaining a lymph node tissue sample and

isolating (purifying) lymphocytes from the sample using Ficoll-Hypaque gradient centrifugation (see page 345 second and third full paragraph). Thereafter, the lymphocytes are cultured and stored (chilled) at about 4C or less (ice water bath (2-6C)) to separate the cells from incubation media containing secreted proteins. The lymphocytes are then disrupted (lysed) using nonionic detergent solution to solubilize cytoplasm without breaking the nuclei and to release newly synthesized proteins and antibodies. The released antibodies are detected using serological assay, which provides a measure of the amount of newly biosynthesized antibodies present in the lymphocytes present in the lymph node tissue sample (see page 346, first paragraph). Choi provides that secretion of newly synthesized antibodies (if secreted from lymphocytic cells) does not begin until 30 minutes after synthesis.

7. Claims 21-23, 25-29, 31, and 33-42 are rejected under 35 U.S.C. 102(b) as being anticipated by Atkinson et al. (Direct Measurement of Antibody Production in Cell Suspensions using ELISA, Journal of Immunological Methods 76: 365-373 (1985)).

Atkinson et al. provide an enzyme-linked immunosorbent assay (ELISA) method for direct measurement of newly synthesized antibody being produced in immune cells, i.e. synthetic capacity, in response to immunogen exposure (anamnestic response to immunization). Atkinson et al. teach obtaining an immune spleen or lymph node sample containing lymphocytes from mice, isolating [nucleated] lymphocytic cells by Ficoll-Hypaque gradient centrifugation, eliminating [secreted] antibody carry-over by multiple washing of the lymphocytes, and disrupting the cells using physical disruption (freeze-

thaw method and sonication) to release newly synthesized antibodies from the cells. After preparation of the sample for assay, Atkinson et al. adds a sample volume of less than 1 ml. (200 ul) into multiple solid phases having one or more antigens immobilized thereto (antigen-coated wells) in a microtiter plate. One or more antibodies (biotinylated anti-mouse immunoglobulin) are also added and coated into the solid phase (see page 367 in its entirety). Atkinson et al. use highly sensitive avidin-biotinylated peroxidase (ABC) reagents and soluble substrate (orthophenylenediamine) to detect and measure the amount of newly synthesized antibodies by ELISA (see page 365, page 366, and 368 in their entirety). According to Atkinson, the lymphocytes should be stored and equilibrated at 4C after initial suspension in order to decrease the rate of antibody synthesis and secretion prior to the method (see page 369 in its entirety). Antibody production by different cell populations can be compared relative to standard controls included in each microtiter plate. Atkinson et al. teach using negative control antigen (irrelevant antigen or bovine serum albumin) as standard (see page 367).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Choi (Biosynthesis and Secretion of Immunoglobulins, Immunoglobulins, pages 345, 346,

348-351 (1981)) or Atkinson et al. (Journal of Immunological Methods 76: 365-373 (1985)) in view of Cox et al. (Kinetics of early immune response induced after parenteral influenza vaccination (Options for the control of influenza III, 561-571 (1996)).

Choi and Atkinson et al. have been discussed supra. Choi and Atkinson et al. differ from the instant invention in failing to teach detecting newly synthesized antibody in peripheral blood samples.

Cox et al. studies kinetics of early immune response induced after immunogen exposure (parenteral influenza vaccination). Cox et al. use different samples including peripheral blood, serum, and oral fluid. In study, in vitro cultures of peripheral blood lymphocytes were obtained and tested for antibody response to the immunogen exposure by detecting or determining for the presence of IgG, IgM, and IgA in the sample. See Abstract, page 565 (The antibody secreting cell response in peripheral blood), and page 567 (The antibody secreting cell response in tonsils).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to perform the method as taught by Choi or Atkinson on peripheral blood samples as taught by Cox because Cox provided that lymphocytes used in the method of Choi and Atkinson, can be obtained and cultured from peripheral blood samples for use in testing antibody production in response to parenteral influenza vaccination; hence, peripheral blood appears to constitute an obvious variation of sample routinely used in the art, upon which lymphocytic cells can be obtained for use in antibody production assays.

9. Claims 24 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Choi (Biosynthesis and Secretion of Immunoglobulins, Immunoglobulins, pages 345, 346, 348-351 (1981)) or Atkinson et al. (Journal of Immunological Methods 76: 365-373 (1985)) in view of Cox et al. (Kinetics of early immune response induced after parenteral influenza vaccination (Options for the control of influenza III, 561-571 (1996)) in view of Sison A V (Laboratory Methods for early detection of HIV-type-1 in Newborns and Infants, (Clinical Microbiology Reviews, 5(3): pp. 238-247 (July 1992)).

Choi and Atkinson et al. have been discussed supra. Choi and Atkinson et al. differ from the instant invention in failing to teach detecting newly synthesized antibodies in neonate or infant blood samples to distinguish between newly synthesized antibodies from the infant and passively transferred maternal antibodies.

Sison teaches determining in vitro antibody production and using ELISA Spot assay to test for immunogenic exposure of infant or neonate to the HIV-1 virus. In practice, Sison teaches obtaining peripheral blood lymphocytes from infants, isolating and culturing the lymphocytic cells in vitro, subjecting the cells to immunogen activation, i.e. pokeweed, and detecting for the production or presence of anti-HIV-1 antibody using HIV-1 antigen coated solid phase (polystyrene wells). Sison uses this test to distinguish between newly synthesized antibodies from the infant and transferred maternal antibodies during pregnancy. See Abstract and page 241, column 1.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to detect newly synthesized antibodies using the method taught by Choi or Atkinson on neonatal or infant samples as taught by Sison because Choi and

Atkinson specifically taught that their methods specifically detect biosynthesis of antibodies in specific cells such as those that are derived from neonatal cells as in the teaching of Sison, where he specifically emphasized the need to separate and distinguish between neonatal derived antibodies and maternally transferred antibodies. One of ordinary skill in the art at the time of the instant invention would have been motivated to detect for the presence of newly synthesized antibody using the method of Choi or Atkinson, in samples obtained from infants or neonates as taught by Sison, because Sison specifically taught that antibody production, i.e. of newly synthesized antibodies, in neonatal [lymphocytic] cells provides specific diagnostic information on immunogen exposure and infection for infants.

10. No claims allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (571) 272-0820. The examiner can normally be reached on Monday, Tuesday, and Thursday, 7:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gailene R. Gabel
Patent Examiner
Art Unit 1641
September 14, 2005